REMARKS

This reply follows an Advisory Action issued February 8, 2011 and is accompanied by a Request for Continued Examination.

Claims 34-36, 38-41, 43-45, and 47-73 are pending in the present patent application. Claims 34, 41, 48, 58, and 65 are amended to incorporate reference to "aza-linked ligands." This feature is described, for example, in paragraph [0027] of the published specification and therefore does not constitute new matter.

Alleged Lack of Enablement

Claims 34-36, 38-41, 43-45, and 47-73, all claims pending in this patent application, stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement with respect to their recitation *in vivo* extracellular administration. Although the Examiner acknowledges that those skilled in the art would be able to produce a biological response in living cells through *in vitro* extracellular administration of the recited compounds, the Examiner contends that those skilled in the art would not be able to produce such a response through *in vivo* extracellular administration. Applicants respectfully request reconsideration and withdrawal of the rejection because the evidence of record indicates that those skilled in the art would be able to achieve at least some measurable biological response through practice of the claimed methods.

The Examiner has yet to meet the Office's burden of showing lack of enablement. In their previous response, Applicants highlighted the fact that the Examiner failed to identify objective evidence indicating that the claimed methods would not produce at least some measurable biological response. Although the Examiner cites a number of publications demonstrating that issues such as cellular uptake of the recited compounds "ha[ve] to be considered" and "should be investigated" (Office Action at page 6), none of these publications indicates that the recited compounds will not perform in the manner contemplated by Applicants' claims. Similarly, although the Office Action cites publications indicating that certain issues relating to the recited compounds "must be addressed before reaching [the] ultimate goal" of using them as "an antisense or antigene drug for sequence-specific modulation of gene expression" (*id.* at page 7), none of these publications indicates

that the compounds do not produce at least some measurable level of the claimed biological response. As will be recognized, the claims do not require that the recited compounds satisfy the rigorous efficacy standards that typically are imposed (by, for example, the FDA) upon commercialized drugs; rather, all that the claims require is that the recited compounds produce some biological response.

The Examiner has responded by improperly attempting to shift the burden of proof to the Applicants, when it still remains with the Office ("it seems that the applicant rather than to point out at the evidence of the presence of the effect of PNAs prefers to point out at the absence of acknowledgement of the absence of the effect." Office Action dated 10/8/10. page 9), and by arguing an unpredictability in the art. To this end, the Examiner offers four references (to Nielsen, Hyrup, Basu, and Ganesh, *et al.*) as evidence that the art of developing pharmacological agents using PNAs is unpredictable.

These references, however, do not demonstrate that developing pharmaceutical agents using PNAs is unpredictable; at best, they indicate that developing an agent with high cell permeability can be difficult. In fact, each of these reference refer to the permeability of PNAs through cell walls, albeit low permeability. Thus, the Examiner appears to be confusing the extent to which Applicants have enabled *some* physiological effect with the extent to which they have enabled preparation of a *commercially viable* pharmaceutical agent. The relevance of the cited references is limited to the hurdles to be overcome in achieving commercially viable pharmacological agents, an embodiment having a significantly higher threshold than those claimed herein. *Engel Industries, Inc. v. Lockformer Co.* , 946 F.2d 1528, 1533 ("[t]he enablement requirement is met if the description enables **any** mode of making and using the claimed invention.") (emphasis added); *CFMT, Inc. v. Yieldup International Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003) (claims directed to "cleaning" semiconductor wafers held to be enabled so long as those skilled in the art could achieve **any level** of cleaning with the claimed invention without undue experimentation) (emphasis added).

That the claimed subject matter is enabled is demonstrated, for example, by the Richelson patent and its disclosure that *in vivo* administration can be achieved, for example, using physiological saline:

> The mode of administering PNA oligomers to living cells can be any mode wherein the administration is extracellular and the administered PNA oligomers engender a sequence specific biological response. For example, PNA oligomers can be applied directly to tissue culture medium when treating cells in vitro or can be administered to an organism when treating cells in vivo. When treating cells in vivo, PNA oligomers can be administered by various routes. Various pharmaceutically acceptable carriers can be used for **in vivo administration** to animals, **including for example physiological saline**, artificial cerebral-spinal fluid, or other known carriers appropriate to specific routes of administration.
>
> For the purpose of this invention, two general routes of administration are provided: intracranial and extracranial. Examples of intracranial routes of administration include but are not limited to intracistemal, intraventricular, and intradural. Examples of extracranial routes of administration include but are not limited to **oral, intravenous, intramuscular, intraperitoneal, subcutaneous, intradermal, topical, or the like**. The route of administration, whether intracranial or extracranial, can depend on a variety of factors, such as treatment environment and therapeutic goals.

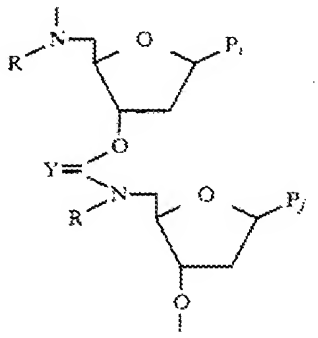
(US 6472209, col. 6, lines 33-55, emphasis added). Indeed, the Richelson patent reports the results of such administration (*see* Example 2, columns 13-15). This is consistent with disclosure in the present application that the claimed compounds can be formulated for topical, oral, inhalation, or parenteral administration, the latter including intravenous drip or subcutaneous, intraperitoneal or intramuscular injection (*see, e.g.,* paragraphs 141-147 of the published specification). And as confirmed by the declaration testimony of Dr. Richard Geary (on the record, as previously submitted on January 10, 2011), those skilled in the art as of the 1991 effective filing date of the instant patent application would have been able to administer the claimed compounds in physiological saline via such routes of administration.

Applicants submit that the Richelson patent and Dr. Geary's testimony (together with the absence of evidence to the contrary) supports the position that those skilled in the art would have been able to practice the claimed methods to at least some measurable extent, such that the rejection under Section 112, first paragraph, should be withdrawn.

Alleged Anticipation

Claims 34-36, 41, 48-51, 58, 59, and 65-68 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,142,047 ("the Summerton patent"). This rejection is improper because the Summerton patent is alleged to be relevant for its disclosure of compounds that have a different structure than those recited in the instant claims.

As described in their last response on this issue, Applicants submit that the Summerton patent does not satisfy all of the requirements necessary for a rejection under 35 USC 102(e). The Examiner asserts that the linkages recited in the instant claims correspond to the linkage used in the following compound in the Summerton patent (Office Action at pages 11-12).



However, the linkage described in the Summerton patent (*i.e.,* -**O**-C(=O)-NR- when Y is oxygen) is a carbamate linkage (a derivative of a carbonic acid, and referred to as such in the Summerton patent), whereas the rejected claims recite an amide linkage (*i.e.*, -**C**-C(=O)-NR-) (a derivative of a carboxylic acid). Thus, there is no anticipation.

Although Applicants do not believe that the Summerton reference anticipates the instant claims, in an effort to advance prosecution, claims 34, 41, 48, 58, and 65 are amended to incorporate reference to aza-linked ligands, thereby distancing them even further from this reference.

Because the structure disclosed in the Summerton patent is different from that recited in the instant claims, the rejection for alleged anticipation is improper and should be withdrawn.

Conclusion

Applicants believe the foregoing constitutes a complete response to the Office Action and submit that all pending claims are in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,

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